Association of Energy Intake and Energy Balance with Postmenopausal Breast Cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

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Abstract

Energy restriction remains one of the most effective ways known to prevent breast cancer in animal models. However, energy intake has not been consistently associated with risk of breast cancer in humans. In a prospective study, we assessed whether energy intake, body size, and physical activity each independently influence breast cancer risk in postmenopausal women and estimated the joint effect of combinations of these individual factors. As part of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, 38,660 women, ages 55 to 74 years and recruited from 10 centers in the United States during 1993 to 2001, were randomized to the screening arm of the trial. At baseline, the women completed a self-administered questionnaire, including a food frequency questionnaire. During follow-up from 1993 to 2003, 764 incident breast cancer cases were ascertained. Women in the highest quartile of energy intake (≥2,084 kcal/d) compared with those in the lowest quartile (<1,316 kcal/d) had a significantly increased risk for breast cancer [multivariate relative risk (RR), 1.25; 95% confidence interval (95% CI), 1.02-1.53; $P_{\text{trend continuous}}$ = 0.03]. Current body mass index (BMI) was also positively and significantly associated with risk (multivariate RR comparing >30 kg/m^2 with <22.5 kg/m^2, 1.35; 95% CI, 1.06-1.70; P_{trend} = 0.01). Women with ≥4 hours/wk of vigorous recreational physical activity had a significantly reduced risk of breast cancer compared with those who reported no recreational physical activity (multivariate RR, 0.78; 95% CI, 0.60-0.99; P_{trend} = 0.15). None of these associations with individual energy balance measures was substantially confounded by the other two measures. When we estimated the joint effect of all three variables, women with the most unfavorable energy balance (the highest energy intake, highest BMI, and least physical activity) had twice the risk (RR, 2.10; 95% CI, 1.27-3.45) of women with the most favorable energy balance (the lowest energy intake, lowest BMI, and most physical activity). Although our estimates of absolute energy intake, based on a food frequency questionnaire, are imperfect, these results suggest that energy intake, in addition to BMI and physical activity may be independently associated with breast cancer risk. In addition, these three aspects of energy balance may act jointly in determining breast cancer risk. (Cancer Epidemiol Biomarkers Prev 2006;15(2):334–41)

Introduction

Breast cancer is the most commonly diagnosed cancer, excluding nonmelanoma skin cancer, among women in the United States (1). As the cause of death in ~40,000 women each year, it is also the second most fatal cancer (1). One of the most persistently hypothesized modifiable risk factors for breast cancer is caloric intake (2, 3). Numerous mammary carcinogenesis studies in animal models have documented that energy restriction reduces proliferative activity and suppresses tumor growth (4, 5). The crucial question raised by these animal experiments is whether such an effect can also occur in humans at levels of energy intake compatible with normal growth and health.

A recent study in Sweden indicated that women hospitalized for anorexia nervosa before age 40, and therefore with abnormally low energy intake, experienced 53% lower breast cancer incidence later in life (6). However, high energy intake has not been consistently linked to increased breast cancer risk in humans (3). Of the 25 studies that have explored the relationship between adult energy intake and breast cancer, 7 (7–13) of 15 case-control studies (7–21) and 2 (22, 23) of 10 prospective studies (22–31) supported positive relationships, with relative risks (RR) ranging from 1.3 to 3.5; eight case-control (14–21) and seven prospective studies (24–27, 29–31) showed no association, and one prospective study (28) reported an inverse association. These discrepancies could be due to inaccurate assessment of energy intake, different ranges of exposure, incomplete control of confounding, or imprecise estimates due to limited sample size.

The relationship between body mass index (BMI) and breast cancer has been examined in >50 studies (32). These investigations show that in western populations, overweight or obesity is associated with increased breast cancer risk in postmenopausal women (32–34) but with decreased risk in premenopausal women (32, 33). The relationship of physical activity to risk of breast cancer has been evaluated in >30 epidemiologic studies (35). High levels of physical activity may reduce breast cancer incidence by 30% to 70% (35).

High energy intake, obesity, and a sedentary lifestyle represent potentially modifiable risk factors for breast cancer in postmenopausal women. However, whether these three components of energy balance influence postmenopausal breast cancer risk independently, or one explains the effect of another, is unknown. In addition, few epidemiologic studies have been able to explore the joint effect of all three factors on breast cancer risk (14).

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We addressed the independent and combined effects of energy intake, BMI, and physical activity on breast cancer incidence in a cohort of women enrolled in the screening arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.

Materials and Methods

Study Design. Subjects in this study were women randomized to the intervention arm of the PLCO Cancer Screening Trial, a randomized multicenter trial to investigate whether screening for prostate, lung, colorectal, and ovarian cancer will reduce cancer-specific incidence and mortality. Details of the study have been described elsewhere (36). Briefly, women ages 55 to 74 years were recruited between November 1993 and July 2001 in 10 U.S. centers. Participants with a personal history of one of the four PLCO cancers or a recent history of screening procedures for one of the cancers or who were currently undergoing treatment for any cancer, except nonmelanoma skin cancer, were excluded from the trial. After approval by the institutional review boards of the U.S. National Cancer Institute and each of the participating centers, each eligible participant provided written informed consent. Women randomized to the intervention arm underwent periodic cancer screening tests, including chest X-ray, flexible sigmoidoscopy, digital rectal examination, cancer antigen 125 screening, and transvaginal ultrasound. Women randomized to the control arm were instructed to follow their usual medical practice.

Study Population. Only women in the screening arm of PLCO were given a food frequency questionnaire (FFQ) at baseline. Of the 77,376 women enrolled in the PLCO trial, a total of 38,660 women were randomized to the screening arm and given a FFQ. Of these, 27,541 women were included in our analyses. Reasons for exclusion included previous diagnosis of cancer, except nonmelanoma skin cancer (n = 2817); unreturned FFQ (n = 6761); missing information for more than seven food items in the FFQ (n = 323); extreme estimates of energy consumption (upper or lower 1% of the distribution; n = 542); and missing data for weight, height, or physical activity (n = 676).

Baseline and Diet Questionnaire. At randomization, all study subjects were asked to complete a self-administered baseline questionnaire that included questions on demographic factors, medical history, and health-related behaviors. In addition, all participants randomized to the PLCO intervention arm were given the PLCO FFQ, designed to be self-administered and to characterize usual dietary intake over the past 12 months (http://www.cancer.gov/prevention/plco/DQX.pdf). Using a grid format, frequency of consumption was asked for 137 food items; in addition, usual portion size (small, medium, or large) was obtained for 77 items. Descriptive data for calculating nutrients and food groups were derived from the two 24-hour recalls administered in the 1994 to 1996 Continuing Survey of Food Intake by Individuals (37), a nationally representative survey conducted during the period when the FFQ was being used. In particular, the cut points between small and medium and between medium and large correspond to the 25th and 75th percentiles for portion sizes reported by participants 51 years or older in the U.S. Department of Agriculture 1994 to 1996 Continuing Survey of Food Intake by Individuals (37). The choice of food items, the wording, and the assumptions for estimating nutrients and food groups for the PLCO FFQ incorporate elements of both cognitive (38, 39) and database (37) research.

Ascertainment and Definition of Breast Cancer Cases. Study subjects were sent annually a mail-in health survey asking whether they had been diagnosed with cancer, and if so, the type of cancer. Incident breast cancer cases were ascertained through self-report in the annual survey, state cancer registries, death certificates, physician reports, and next-of-kin reports for deceased individuals. Pathology reports were sought for all cases, and 73% of ascertained breast cancer cases were confirmed through medical record review. The results from subanalyses excluding unconfirmed cases (27% of total cases) and *in situ* cases (13% of total cases) did not differ from the results for all cases; therefore, we included all ascertained cases in our final analyses to increase the statistical power.

Assessment of Energy Intake, Height, BMI, and Physical Activity. Intake of total energy was estimated by summing over all foods the product of the frequency of consumption of each food, the usual portion size in grams, and the energy content per gram (37). Height and current body weight were obtained at enrollment through self-report. The BMI was calculated by dividing weight in kilograms by the square of height in meters. Recreational physical activity was assessed at enrollment by asking participants the following question: ''About how many hours do you spend in vigorous activities, such as swimming, brisk walking, etc.?'' Possible answers were 0, <1, 1, 2, 3, or $\geq$ 4 hours/wk.

Statistical Analysis. Our main analysis was based on energy intake stratified by quartiles. We also subdivided energy intake by 300 kcal/d increments. BMI was divided into five categories (<22.5, 22.5-24.9, 25.0-27.4, 27.5-29.9, and $\geq$ 30.0 kg/m^2), which incorporated the definitions of overweight (25-29.9 kg/m^2) and obesity ($\geq$30 kg/m^2) proposed by WHO. Physical activity was stratified according to the categories on the questionnaire, and height was divided into four categories (<1.58, 1.58 to <1.63, 1.63 to <1.68, and $\geq$1.68m). Dietary fat and alcohol intake, derived from the PLCO FFQ (37), were adjusted for total energy intake using a regression analysis (40).

To determine the associations between exposures of interest and breast cancer, age-adjusted and multivariate Cox proportional hazards regression, using age as the underlying time metric (41), was used. Covariates included risk factors consistently associated with breast cancer in the literature. Unless otherwise specified, multivariate models included study center, race, height, history of breast cancer in any first-degree relative, personal history of benign breast disease, age at menarche, age at first live birth, parity, age at menopause, menopausal hormone therapy, and education. To evaluate whether the association between energy intake and breast cancer was linear, we also ran a restricted cubic regression spline with four knots, located at the 5th, 25th, 75th, and 95th percentiles of energy intake (42). The null hypothesis is that the relationship between the log of the adjusted hazard ratio for breast cancer and total calories is linear, and $P < 0.05$ supports a nonlinear relationship.

Tests for linear trend were conducted by treating the median values of each exposure category as a single continuous variable in the model. To evaluate effect modification, stratum-specific risks were examined, and multiplicative interaction terms were added to a fully adjusted model. All Ps were two sided, and $\alpha < 0.05$ indicated statistical significance. SAS statistical software, version 8.2 (SAS Institute, Inc., Cary, NC), was used for all analyses.

Results

In this cohort of women, median reported energy intake was 1,656 kcal/d, with an interdecile range of 1,043 to 2,552 kcal/d. Women with higher energy intake tended to be heavier and more physically active than women with lower energy intake (Table 1). In addition, women consuming more calories were older at their first birth, older at the onset of menopause, and

Table 1. Age-standardized baseline characteristics of study participants in relation to total energy intake

Characteristic	Quartile of energy intake			
	Q1 (n = 6,885)	Q2 (n = 6,885)	Q3 (n = 6,886)	Q4 (n = 6,885)
Range of energy intake (kcal/d)	<1,316	1,316-1,656	1,657-2,083	≥2,084
Age (y)*	63.1 ± 5.3	63.0 ± 5.4	63.0 ± 5.4	62.5 ± 5.3
BMI (kg/m^2)*	26.5 ± 5.1	26.7 ± 5.2	27.0 ± 5.4	27.8 ± 5.8
Height (m)*	1.63 ± 0.07	1.63 ± 0.06	1.63 ± 0.07	1.64 ± 0.07
Recreational physical activity (%), h/wk				
Never	17.7	14.3	14.2	15.0
<1	19.8	18.2	18.3	17.9
1	12.2	12.1	12.0	11.7
2	16.1	16.9	17.7	16.7
3	15.7	17.1	17.3	16.4
≥4	18.5	21.4	20.5	22.3
Family history of breast cancer† (%)	13.6	14.4	13.7	13.9
Mammography in past 3 y (%)				
Never	8.8	7.7	8.2	9.7
Once	18.9	18.2	18.2	19.7
More than once	72.3	74.1	73.6	70.6
Age at menarche (%), y				
<11	19.7	19.1	19.8	20.1
12-13	53.9	56.0	54.7	53.7
14-15	21.6	20.8	21.5	21.5
≥16	4.7	4.1	4.0	4.7
Age at first birth (%), y				
<19	18.7	15.0	14.8	15.9
20-24	46.9	49.1	47.7	47.5
25-29	19.8	20.6	21.0	20.0
≥30	6.0	6.4	7.3	7.4
Parity (%)				
0	8.6	8.9	9.2	9.3
1	7.0	6.6	7.2	7.4
2	24.6	24.0	23.9	22.1
3	26.2	25.7	25.0	24.6
4	16.3	16.9	16.8	17.4
≥5	17.3	17.9	17.9	19.2
Age at menopause (%), y				
<40	15.5	13.3	13.0	12.8
40-44	13.9	14.6	15.5	13.2
45-49	24.0	23.2	22.2	23.9
50-54	36.6	37.6	39.3	38.2
≥55	10.0	11.3	12.0	11.9
Menopausal hormone therapy (%)				
Current user	52.0	53.1	52.6	49.6
Past user	15.9	15.4	16.3	16.4
Dietary fat (g/d)*,‡	49.1 ± 10.3	54.1 ± 10.6	54.8 ± 10.6	51.3 ± 11.1
Alcohol (g/d)*,‡	4.91 ± 7.99	6.30 ± 10.46	7.11 ± 12.14	7.42 ± 14.81

NOTE: All values (except age) are directly standardized to the age distribution of the study population.
*Mean ± SD.
†Any first-degree relative with breast cancer.
‡Adjusted for energy using regression analysis.

less likely to be currently using hormone replacement therapy than women consuming fewer calories (Table 1). Lighter women tended to be more physically active, with ≥4 hours of vigorous recreational physical activity per week reported by 27.8% of women with a BMI < 25.0 kg/m^2, 19.0% of overweight women (25-29.9 kg/m^2), and 10.7% of obese women (≥30 kg/m^2).

Energy intake was positively, but weakly, associated with both current BMI (Spearman partial correlation coefficient r, controlled for physical activity = 0.10) and physical activity (Spearman partial r, controlled for BMI = 0.06). Physical activity, however, was moderately and inversely associated with BMI (Spearman partial r, controlled for energy intake = −0.26). Current BMI was strongly correlated with current weight (Spearman r = 0.91) and weakly correlated with height (Spearman r = −0.06).

During 9.3 years (median = 4.9 years) and 138,654 person-years of follow-up, 764 women developed incident breast cancer. Energy intake was significantly associated with a modest increase in breast cancer risk. Women in the highest quartile of energy intake had a multivariate RR of breast cancer of 1.25 [95% confidence interval (95% CI), 1.02-1.53; P_{trend} = 0.064] compared with women in the lowest quartile (Table 2). This association was not noticeably attenuated (RR, 1.23; 95% CI, 1.01-1.51; P_{trend} = 0.085) when we additionally adjusted for BMI, treated as a continuous variable to optimize control of confounding, and physical activity (Table 2). Assigning individual women to percentile of energy intake based on the distribution among women in the same 5-year age group produced similar results (RR between extreme quartiles for multivariate model 1, 1.22; 95% CI, 1.00-1.50; P_{trend} = 0.103). Excluding the 98 breast cancer cases ascertained during the first year of follow-up (RR comparing extreme quartiles for multivariate model 1, 1.26; 95% CI, 1.01-1.56; P_{trend} = 0.086), excluding the 209 cases not confirmed through medical record review (RR, 1.27; 95% CI, 0.99-1.61; P_{trend} = 0.093), or excluding the 108 carcinoma *in situ* cases (RR, 1.26; 95% CI, 1.01-1.57; P_{trend} = 0.061) also did not change the relationship.

To explore further the dose-response relationship, we stratified energy intake into 300 kcal/d increments. Breast cancer risk rose steadily over the range of reported energy intakes (~1,000 to ~3,000 kcal/d), and the trend was significant

Table 2. RRs of breast cancer in relation to energy intake, BMI, recreational physical activity, and height

	Cases	Person-years	RR (95% CI)		
			Age-adjusted model	Multivariate model 1*	Multivariate model 2
Energy intake (kcal/day)					
Q1 (<1,316)	166	34,184	1.0	1.0	1.0 †
Q2 (1,316-1,657)	198	34,662	1.18 (0.96-1.45)	1.14 (0.92-1.40)	1.14 (0.93-1.40)
Q3 (1,658-2,083)	179	35,156	1.05 (0.85-1.30)	0.98 (0.79-1.21)	0.97 (0.78-1.20)
Q4 (≥2,084)	221	34,652	1.33 (1.09-1.63)	1.25 (1.02-1.53)	1.23 (1.01-1.51)
P_{trend}			0.014	0.064	0.085
BMI (kg/m^2)					
≤22.4	139	27,694	1.0	1.0	1.0 ‡
22.5-24.9	177	31,280	1.13 (0.91-1.41)	1.20 (0.96-1.51)	1.20 (0.96-1.50)
25.0-27.4	168	29,791	1.12 (0.90-1.40)	1.24 (0.99-1.56)	1.22 (0.97-1.54)
27.5-29.9	114	18,554	1.22 (0.95-1.56)	1.42 (1.11-1.83)	1.39 (1.08-1.79)
≥30.0	166	31,335	1.07 (0.85-1.34)	1.35 (1.06-1.70)	1.29 (1.01-1.64)
P_{trend}			0.673	0.014	0.042
Recreational physical activity (h/wk)					
0	113	20,623	1.0	1.0	1.0§
<1	129	25,085	0.95 (0.74-1.22)	0.89 (0.69-1.15)	0.91 (0.70-1.17)
1	95	16,582	1.05 (0.80-1.38)	0.96 (0.73-1.26)	0.98 (0.74-1.28)
2	132	23,646	1.02 (0.79-1.31)	0.90 (0.70-1.16)	0.93 (0.72-1.20)
3	151	23,480	1.17 (0.92-1.50)	1.02 (0.79-1.30)	1.06 (0.82-1.36)
≥4	144	29,238	0.90 (0.70-1.15)	0.78 (0.61-0.99)	0.81 (0.63-1.05)
P_{trend}			0.851	0.153	0.302
Height (m)					
<1.58	165	35,586	1.0	1.0	1.0‖
≥1.58, <1.63	225	41,776	1.17 (0.96-1.43)	1.16 (0.95-1.43)	1.16 (0.94-1.42)
≥1.63, <1.68	221	37,162	1.30 (1.06-1.59)	1.28 (1.04-1.58)	1.28 (1.04-1.58)
≥1.68	153	24,130	1.40 (1.12-1.74)	1.33 (1.06-1.68)	1.33 (1.05-1.67)
P_{trend}			0.002	0.011	0.012

*Multivariate model 1 adjusted for study center, race (White, Black, Hispanic, Asian, Pacific Islander, American Indian/Alaskan Native), height (continuous), family history of breast cancer (yes or no), history of benign breast disease (yes or no), age at menarche (≤11, 12-13, 14-15, ≥16 y), age at first birth (≤19, 20-24, 25-29, ≥30 y, or nulliparous), parity (0, 1, 2, 3, 4, ≥5 live births), age at menopause (<40, 40-44, 45-49, 50-54, ≥55 y), menopausal hormone therapy (never used, 1-5 y of use, 6-9 y of use, ≥10 y of use), and education (≤11 y, 12 y, or high school equivalent; post-high school; college graduate; or postgraduate).

†Additionally adjusted for BMI (continuous) and physical activity (all categories included in questionnaire).

‡Additionally adjusted for energy intake (continuous) and physical activity (all categories included in questionnaire).

§Additionally adjusted for energy intake (continuous) and BMI (continuous).

‖Additionally adjusted for energy intake (continuous), BMI (continuous), and physical activity (all categories included in questionnaire).

(P_{trend} = 0.019; Table 3). Relative to women consuming 1,500 to 1,799 kcal/d (median for study population = 1,656 kcal/d), the multivariate RR of breast cancer for women reporting ≥3,300 kcal/d was 1.49 (95% CI, 0.93-2.38). A restricted cubic regression spline model inferred that the relationship between breast cancer risk and energy intake was linear (P = 0.75). Addition of BMI (continuous form) and physical activity to the spline model indicated minimal confounding. Alcohol and dietary fat, both sources of calories, have been linked to increased breast cancer risk, with the evidence more compelling for alcohol. However, the association between energy and breast cancer was not weakened by the addition to multivariate model 1 of either energy-adjusted alcohol intake (RR for ≥3,300 kcal/d relative to 1,500-1,799 kcal/d, 1.49; 95% CI, 0.93-2.37; P_{trend} = 0.026) or energy-adjusted fat intake (RR, 1.61; 95% CI, 0.99-2.60; P_{trend} = 0.018). Furthermore, the relationship was not attenuated by addition of a measure of recent mammography screening (RR, 1.51; 95% CI, 0.95-2.41; P_{trend} = 0.018).

We also examined energy intake attributable to metabolic size by using a formula for kcal of resting energy expenditure (43). Using multivariate model 1, the RR of breast cancer comparing extreme quartiles of kcal of resting energy expenditure was 1.16 (95% CI, 0.94-1.43).

Current BMI was also significantly and positively associated with breast cancer risk (Table 2). Compared with women with a BMI < 22.5 kg/m^2, overweight and obese women had multivariate RRs of 1.42 and 1.35, respectively (P_{trend} = 0.014). This relationship was slightly attenuated but remained significant when additionally adjusted for energy intake and physical activity. The association between BMI and postmenopausal breast cancer did not differ across strata of height ($P_{interaction}$ = 0.71). Among women <158 cm, the multivariate RRs of postmenopausal breast cancer for increasing tertiles of BMI (<24.1, 24.1-28.3, and ≥28.3 kg/m^2) were 1.0, 1.19, and 1.38 (95% CI, 0.92-2.06; P_{trend} = 0.02), respectively. Among women 158 to <163 cm, the multivariate RRs were 1.0, 1.34, and 1.41 (95% CI, 1.01-1.98; P_{trend} = 0.34), respectively; among women ≥163 cm, they were 1.0, 1.06, and 1.16 (95% CI, 0.89-1.52; P_{trend} = 0.24), respectively. The relationship of BMI to postmenopausal breast cancer risk was stronger ($P_{interaction}$ = 0.04) among women who had never used hormone replacement therapy (≥30 versus <22.5 kg/m^2; multivariate RR, 2.00; 95% CI, 1.20-2.32) than among women who had ever used hormone replacement therapy (≥30 versus <22.5 kg/m^2; multivariate RR, 1.08; 95% CI, 0.82-1.43).

Breast cancer risk among women engaging in vigorous recreational physical activity for ≥4 hours/wk was significantly decreased, relative to women never (0 hours/wk) engaging in vigorous recreational activity (multivariate RR, 0.78; 95% CI, 0.61-0.99), although a clear trend was not apparent (P_{trend} = 0.15; Table 2). The relationship was only modestly weakened by the addition of energy intake and BMI to the model. When women who were physically active for ≥4 hours/wk were compared with all the less active women combined, the multivariate RR was 0.82 (95% CI, 0.68-0.98).

In both age-adjusted and multivariate analyses, a significant positive relationship was evident between height and breast cancer risk (P_{trend} = 0.002 and 0.011, respectively; Table 2). Comparing extreme categories of height, the multivariate RR of breast cancer was 1.33 (95% CI, 1.06-1.68).

We examined the joint effect of energy intake and body size and of energy intake and physical activity to breast cancer risk (Table 4). In both cases, interaction was not statistically significant; the Ps for the two-way interaction terms for energy intake and BMI and for energy intake and physical activity

Table 3. RRs of breast cancer in relation to energy intake, using increments of 300 kcal/d

Energy intake (kcal/d)	Cases	Person-years	RR (95% CI)		
			Age-adjusted	Multivariate model 1*	Multivariate model 2 †
<900	26	6,445	0.79 (0.52-1.19)	0.88 (0.58-1.33)	0.88 (0.58-1.33)
900-1,199	86	17,605	0.95 (0.73-1.23)	1.00 (0.77-1.30)	1.00 (0.77-1.31)
1,200-1,499	163	28,791	1.10 (0.88-1.37)	1.12 (0.90-1.40)	1.13 (0.90-1.40)
1,500-1,799	155	30,104	1.0	1.0	1.0
1,800-2,099	119	22,057	1.05 (0.83-1.33)	1.03 (0.81-1.30)	1.02 (0.81-1.30)
2,100-2,399	91	14,898	1.19 (0.92-1.55)	1.17 (0.90-1.52)	1.17 (0.90-1.51)
2,400-2,699	55	8,609	1.26 (0.92-1.71)	1.25 (0.92-1.70)	1.23 (0.90-1.67)
2,700-2,999	31	4,683	1.30 (0.88-1.91)	1.30 (0.88-1.91)	1.29 (0.87-1.89)
3,000-3,299	18	2,661	1.33 (0.82-2.17)	1.35 (0.83-2.20)	1.31 (0.81-2.14)
≥3,300	20	2,801	1.41 (0.89-2.25)	1.49 (0.93-2.38)	1.46 (0.91-2.32)
P_{trend}					
Medians of categories			0.005	0.019	0.032
Continuous ‡			0.003	0.031	0.048

*Multivariate model 1 adjusted for study center, race (White, Black, Hispanic, Asian, Pacific Islander, American Indian/Alaskan Native), height (continuous), family history of breast cancer (yes or no), history of benign breast disease (yes or no), age at menarche (≤11, 12-13, 14-15, ≥16 y), age at first birth (≤19, 20-24, 25-29, ≥30 y, or nulliparous), parity (0, 1, 2, 3, 4, ≥5 live births), age at menopause (<40, 40-44, 45-49, 50-54, ≥55 y), menopausal hormone therapy (never used, 1-5 y of use, 6-9 y of use, ≥10 y of use), and education (≤11 y, 12 y, or high school equivalent; post-high school; college graduate; or postgraduate).
†Additionally adjusted for BMI (continuous) and physical activity (all categories included in questionnaire).
‡The test for trend was applied to energy as a continuous variable.

were 0.56 and 0.68, respectively. Breast cancer risk consistently increased with energy intake, at both low and high levels of BMI and at both low and high levels of physical activity. For women not only in the highest quartile of energy intake but also currently obese, the multivariate RR of breast cancer reached 1.6. To ensure that the breast cancer risks by energy intake and BMI were fully controlled for BMI, we added BMI as a continuous variable to the model; the results were essentially unchanged. In addition, adjustment of the model for physical activity did not affect the results (multivariate RR, 1.59; 95% CI, 1.13-2.24). For women in the highest quartile of energy intake and also not engaging in vigorous physical activity at least 4 hours/wk, the multivariate RR reached 1.7. After controlling for BMI, treated as a continuous variable, this finding was essentially unchanged (multivariate RR, 1.74; 95% CI, 1.14-2.66).

We also examined the combined effect of BMI and physical activity on breast cancer risk. Compared with women with normal weight (BMI < 25 kg/m^2) who also engaged in vigorous physical activity for ≥4 hours/wk, breast cancer risk was significantly elevated for women who reported <4 hours of weekly physical activity and were either overweight (multivariate RR, 1.36; 95% CI, 1.05-1.75) or obese (multivariate RR, 1.34; 95% CI, 1.01-1.76).

When we jointly evaluated energy intake, BMI, and physical activity, women with the most unfavorable energy balance (the highest energy intake, highest BMI, and lowest physical activity level) had the highest risk for developing breast cancer (Fig. 1). Relative to women who fell into the lowest quartile of energy intake, had a BMI of <30 kg/m^2, and reported engaging in ≥4 hours/wk of vigorous physical activity, breast cancer risk was doubled in women who fell into the highest quartile of energy intake, had a BMI of ≥30 kg/m^2, and reported <4 hours/wk of physical activity (multivariate RR, 2.10; 95% CI, 1.27-3.45). This result was not materially changed when we additionally adjusted for mammography screening in the past 3 years (multivariate RR, 2.12; 95% CI, 1.29-3.50). The three-way interaction term for energy intake, BMI, and physical activity was not statistically significant (P = 0.98), which indicated that the relationship of breast cancer risk to energy intake did not differ substantially among women with different BMIs and physical activity levels.

Table 4. Multivariate relative risks of breast cancer in relation to energy intake and BMI and to energy intake and recreational physical activity, considered concurrently

Quartile of energy intake (kcal/d)	BMI*, RR (95% CI)		
	<25 kg/m^2	25-29 kg/m^2	≥ 30 kg/m^2
Q1 (<1,316)	1.0	1.20 (0.85-1.68)	1.10 (0.71-1.68)
Q2 (1,316-1,657)	1.16 (0.85-1.58)	1.38 (1.00-1.91)	1.13 (0.74-1.71)
Q3 (1,658-2,083)	0.93 (0.68-1.29)	1.11 (0.79-1.55)	1.25 (0.85-1.83)
Q4 (≥2,084)	1.20 (0.87-1.65)	1.37 (0.99-1.88)	1.60 (1.13-2.25)
$P_{interaction}$ = 0.56			

Quartile of energy intake (kcal/d)	Recreational physical activity*, RR (95% CI)	
	≥4 h/wk	<4 h/wk
Q1 (<1,316)	1.0	1.44 (0.94-2.21)
Q2 (1,316-1,657)	1.30 (0.78-2.15)	1.60 (1.05-2.45)
Q3 (1,658-2,083)	1.13 (0.67-1.91)	1.37 (0.89-2.10)
Q4 (≥2,084)	1.53 (0.94-2.48)	1.74 (1.14-2.65)
$P_{interaction}$ = 0.68		

*Multivariate model 1 adjusted for study center, race (White, Black, Hispanic, Asian, Pacific Islander, American Indian/Alaskan Native), height (continuous), family history of breast cancer (yes or no), history of benign breast disease (yes or no), age at menarche (≤11, 12-13, 14-15, ≥16 y), age at first birth (≤19, 20-24, 25-29, ≥30 y, or nulliparous), parity (0, 1, 2, 3, 4, ≥5 live births), age at menopause (<40, 40-44, 45-49, 50-54, ≥55 y), menopausal hormone therapy (never used, 1-5 y of use, 6-9 y of use, ≥10 y of use), and education (≤11 y, 12 y, or high school equivalent; post-high school; college graduate; or postgraduate).

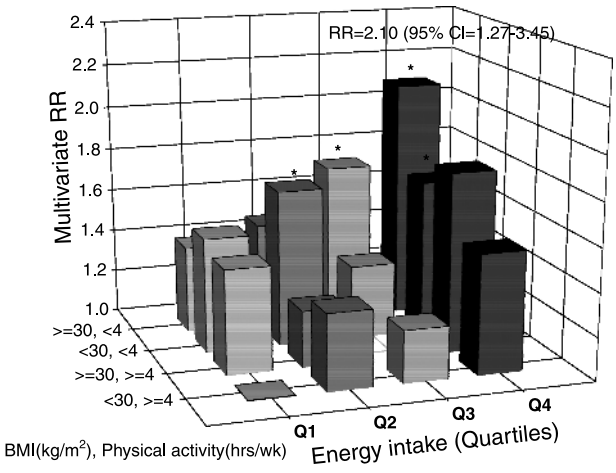

Figure 1. Multivariate relative risks of breast cancer in relation to energy intake, BMI, and recreational physical activity, considered concurrently. Multivariate model adjusted for study center, race (White, Black, Hispanic, Asian, Pacific Islander, American Indian/Alaskan Native), height (continuous), family history of breast cancer (yes or no), history of benign breast disease (yes or no), age at menarche (≤11, 12-13, 14-15, ≥16 years), age at first birth (≤19, 20-24, 25-29, ≥30 years, or nulliparous), parity (0, 1, 2, 3, 4, ≥5 live births), age at menopause (<40, 40-44, 45-49, 50-54, ≥55 years), menopausal hormone therapy (never used, 1-5 years of use, 6-9 years of use, ≥10 years of use), and education (≤11 years, 12 years, or high school equivalent; post-high school; college graduate; or postgraduate). *95% CI excludes 1.0.

Discussion

In a large prospective study, we found that increasing energy intake, in a range typical of U.S. diets, was positively and significantly associated with risk of breast cancer, even after controlling for the effects of BMI and physical activity. Breast cancer risk rose with energy intake at low and high levels of BMI and at low and high levels of physical activity. Because energy intake, BMI, and physical activity were each independently associated with breast cancer risk, we estimated joint effects of these variables. Women with an unfavorable energy balance (high energy intake, high BMI, and low physical activity) had twice the risk of women with a favorable energy balance.

Our findings are compatible with two prospective studies that reported positive, although nonsignificant, associations between energy intake and breast cancer (22, 23). In a study from Norway (22), women in the highest quartile of energy intake had an increased breast cancer risk compared with women in the lowest quartile (multivariate RR, 1.37; 95% CI, 0.95-1.98). In a small U.S. cohort (n = 590 women) followed for 15 years, breast cancer risk more than doubled for every 500 kcal/d increment in total energy intake (23). Our results also agree with those from seven case-control studies (7–13) that showed positive relationships between breast cancer and energy intake. It is possible that in the case-control studies, recall of past diet by the cases was biased or energy intake was assessed closer in time to the etiologically relevant period of exposure. In contrast to these supportive studies, our results are not consistent with seven prospective (24–27, 29–31) and eight case-control (14–21) studies that reported no association between energy intake and breast cancer. One prospective study from Finland found an inverse relationship but included a small number of cases and controlled only for age (28).

The adverse influence of high energy intake on human mammary carcinogenesis has been inferred from animal models of energy restriction (4, 5, 44), which fairly consistently show that diminished caloric intake, regardless of energy source, leads to fewer and/or smaller mammary tumors. Human data relating energy restriction to subsequent breast cancer risk are limited, and results are not totally consistent. In an international comparison of food availability data, per capita total energy was positively correlated (r = 0.56) with breast cancer mortality (45). A recent Swedish study reported a statistically significant ~50% decrease in breast cancer risk among women hospitalized for anorexia nervosa earlier in life (6). A Norwegian study found that breast cancer incidence was reduced among the cohort of women who, as adolescents, had experienced famine during the 1940 to 1945 wartime conditions (46). In contrast, a Dutch study found an increased risk of breast cancer in children and young women who survived a short, intense famine during 1944 to 1945 (47). Indirect support for an energy effect is also provided by consistent epidemiologic evidence linking height (33, 34), which is partially determined by early energy intake, and adiposity (32–34), which is related to adult energy intake, to increased risk of breast cancer.

Reasons for our positive findings regarding energy intake and breast cancer are speculative. The relative validity of the FFQ that we used may have contributed to our observation of a modest adverse effect for excess energy intake. Measurement of total energy intake using a FFQ is difficult and imperfect, but some variation in the validity of different instruments may exist. In designing the PLCO FFQ, attention was paid to assessing calories and fat, updating the food list, obtaining realistic portion sizes, and rationally assigning nutrient values (37, 38). In addition, a cognitive approach (38, 39) was used to develop wording and formatting that would optimize comprehensibility, ease of completion, and participation (48). Although the PLCO FFQ has not been directly compared with dietary recalls or records, in a measurement model, the correlation between total energy intake calculated from four 24-hour dietary recalls and assessed by the National Cancer Institute Health Habits and History Questionnaire (49) or the National Cancer Institute Dietary History Questionnaire (50), the two FFQs most similar to the PLCO FFQ, was 0.45 and 0.48, respectively, a relatively high agreement, suggesting reasonable validity. Nevertheless, this correlation could be misleadingly high due to the wide range in ages within the validation study population and correlated error between the FFQs and the dietary recalls used as reference instruments (51, 52).

The PLCO FFQ seemed to perform reasonable in assessing energy intake. As would have been predicted, energy intake increased with both BMI and physical activity in our study population. With 137 food items, 77 of which asked about usual portion size, the FFQ captured a relatively wide distribution of energy intake; the interdecile range was 1,043 to 2,552 kcal/d. Identifying women with especially high energy intake may have enhanced our ability to detect a positive association. Although women consuming ~2,500 kcal/d had a breast cancer risk of 1.25, relative to women consuming 1,500 to 1,799 kcal/d, risk rose above 1.3 for women consuming ≥3,000 kcal/d and above 1.4 for women consuming ≥3,300 kcal/d. Because of differences in assessment instruments and databases, estimates of absolute energy intake may not be strictly comparable among studies. However, 6 (7–11, 13) of the 10 breast cancer studies that have been able to identify women with energy intakes of ≥2,500 kcal/d (7–11, 13, 19, 20, 26, 28) have reported a positive relationship between total energy intake and breast cancer. Possibly, in an energy-replete population, a careful assessment of the higher end of energy intake may be necessary to detect a potential breast cancer association.

We considered whether bias might explain our findings. When we excluded women whose breast cancer was diagnosed during the first year of follow-up or was not confirmed by medical records, results were essentially unchanged. Thus, neither preclinical breast cancer nor inaccurate self-reports of breast disease influenced our findings. Although it is not known how energy intake is related to mammography screening behavior, obese women are less likely to undergo mammography screening than normal-weight women (53). Thus, the positive relationship between energy intake and breast cancer is unlikely to be due to detection bias because diagnosis of breast cancer would be reduced in the heaviest women. Furthermore, none of our major results was changed when we additionally adjusted for history of mammography screening. Reporting bias may exist because women who underreport weight may also underreport energy intake and overreport physical activity. However, reporting bias is unlikely to explain our results unless linked to breast cancer status, and our questionnaires were completed before any diagnosis of disease.

We also considered whether uncontrolled confounding might explain our results. Because BMI has been consistently associated with increased breast cancer risk in postmenopausal women (32–34) and was positively correlated with energy intake ($r = 0.10$) in our study population, residual confounding can not be ruled out. However, confounding was minimal, and the energy-breast cancer relationship persisted even after adjusting for BMI using a continuous variable. Although physical activity was not assessed in detail, it did not seem to substantially confound the energy-breast cancer association and would have tended to weaken it if not adequately controlled. Finally, energy intake, BMI, and physical activity were assessed using a single self-report, which may not always have represented long-term behavior patterns and likely contained some inaccuracies. Deliberate underreporting and overreporting would also lead to imprecise estimates of exposure. Such random error tends to attenuate associations and raises the possibility that the associations with breast cancer that we are reporting are underestimates of the underlying relationships.

The simultaneous inclusion of energy intake, BMI, and physical activity in a multivariate model was initially of concern because the imbalance between energy intake and expenditure determines BMI. However, differences in relevant time periods, variation in body composition, imprecision in measurement, and unmeasured components of energy balance, such as occupational activity and leisurely recreational activity, enabled us to consider all three energy balance variables concurrently. It is also conceivable that in this older, more sedentary population, variation in metabolic efficiency contributes to differences in energy balance.

Our findings concerning BMI and postmenopausal breast cancer agree with previous epidemiologic studies (32). In a pooled analysis of seven prospective studies, including 3,208 postmenopausal breast cancer cases, risk increased to 1.26 and leveled off when BMI exceeded 28 kg/m^2 (33), which is compatible with our results.

Our findings regarding physical activity and breast cancer are also consistent with the majority of previous studies (35). A recent review by Hardman (54) suggested that, in general, breast cancer risk was decreased at ~4 hours/wk of moderate activity, which tends to concur with our results. The ~20% reduction in breast cancer risk for the highest level of physical activity reported in our study is somewhat weaker than the 30% to 70% reduction seen in previous studies (35), which may be due to a less comprehensive assessment of physical activity in our cohort.

Energy intake may modulate breast cancer risk through a complex dynamic interplay of the hormones that control energy balance (55). High energy intake is associated with increased availability of insulin-like growth factor-I (56, 57). The growth hormone/insulin-like growth factor-I axis may play an etiologic role (58). Higher energy intake may also increase blood insulin levels (59), and enhanced insulin secretion has been associated with an increased risk of breast cancer (60). Additional potential biological mechanisms for energy intake involve steroid hormones, chronic inflammation, immune function, and oxidative stress (61). Because energy intake, BMI, and physical activity were independently associated with breast cancer risk in our cohort, it is conceivable that these three lifestyle-related exposures influence breast cancer through different metabolic pathways.

In our study population, height was as persuasively related to breast cancer risk as energy intake, BMI, and physical activity. Our finding of a positive association between height and breast cancer risk is consistent with the hypothesis that variation in height reflects not only genetic factors but also differences in energy intake and dietary patterns early in life (62). That we observed positive relationships of both height and energy intake to breast cancer risk suggests that the effect of elevated energy intake on breast carcinogenesis may be a continuous and cumulative process throughout the entire life.

In summary, our results suggest that energy intake, BMI, and physical inactivity are each independently and positively associated with breast cancer risk. A positive energy balance, whether generated by increased energy intake or decreased energy expenditure or indicated by excess body weight, adversely influences breast cancer risk. In our study population, when all three factors were jointly considered, risk was doubled among women with the least favorable energy balance relative to women with the most favorable energy balance. It is not obvious how to facilitate the adoption and maintenance of a lifestyle characterized by reduced energy intake, increased physical activity, and decreased body weight; but these lifestyles, although resistant to change, are modifiable. Further research on the biological mechanisms underlying the energy balance-breast cancer relationship might suggest alternative interventions. However, our results suggest that individual and public health efforts directed towards achieving energy balance may substantially reduce breast cancer risk.

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